ing Information Processing Speed Cognitive Impairment: Clinical Research Dichotomy

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2015

tial body of research evidence is indicative of disproportionately slowed information processing speed ulti-trial, computer-based, neuroimaging- and electroencephalography-based reaction time (RT) tests se and mild cognitive impairment (MCI). However, in what is arguably a dichotomy between research practice, RT associated with different brain functions is rarely assessed as part of their diagnosis. Indeed, aken to perform a single, specific task, commonly the Trail making test (TMT), is measured. In clinical ere can be a failure to assess adequately the integrity of the rapid, serial information processing and for efficient, appropriate, and safe interaction with the environment. We examined whether a typical ask could at least match the TMT in differentiating amnestic MCI (aMCI) from cognitively healthy As aMCI is a heterogeneous group, typically containing only a proportion of individuals for whom early stages of dementia, we examined the ability of each test to capture intra-individual variation in sults indicate that as well as significant slowing in performance of the operations involved in TMT part ndividuals with aMCI also experience significant slowing in RT compared to controls. The results also -typical RT tests may be superior to the TMT in differentiating between cognitively healthy aging and

r of changes to everyday func-
at least in part, some of the signs,
anges in behavior related to aMCI
isproportionate slowing is associ-
tion of driving [17, 18], mortality
-dwelling older adults [19], func-
n activities of daily living [19, 20],
], and outcome after stroke [22].
evance to potential clinical impact
the substantial body of evidence
elationship between RT and some
's structural integrity. Information
as indicated by RT (i.e., the time
he presentation of a stimulus and
onse), measured over a number of
based stimulus response tests, can
oral 'marker' of neurophysiologi-
xample, disruption to white matter
rity and change in neurotransmit-
with disproportionate slowing of
dividual variability in RT [1, 8,
therefore this link between struc-
nal integrity and behavioral RT
ntial for simple RT tests as valid
ssment of diagnosis, status, stage,
nterventional success in dementia
rs [31].
ith appropriate methodological
e used to assess the integrity of
f brain function including atten-
sual processing, and cognition, at
ocessing and in response to differ-
resource demands [8]. Indeed, the
tia-related research studies exam-
n to brain structure and function
iques such as DTI, EEG, MRI,

Clinically, despite this research evidence, information processing speed tends *not* to be assessed using a variety of function-specific, computer-based, multi-trial RT tests. Although a variety of RT-based tests are available and in use clinically, in some cases information processing speed is assessed by measuring the time taken to perform a given task, namely using a stop-watch to measure the single trial performance of the pen and paper Trail Making Test (TMT) [32–38]. The TMT is a test administered in two parts. In Trails A, individuals are required to connect a series of consecutively numbered circles that are presented in a random pattern on the paper: a task typically described as probing functions such as speed of processing in relation to attention, visual scanning and search, number recognition, numeric sequencing, and motor speed. In Trails B, individuals are required to connect a series of numbered and lettered circles alternating between the two sequences; a task typically described as probing the efficiency of set shifting, mental flexibility, executive function, divided attention, attention switching, visual search set shifting, simultaneous maintenance of two sequences, working memory and cognitive flexibility; arguably a measure of information processing speed in relation to multiple high level, non-specific functions [33, 34, 39]. TMT performance, in both parts A and B, is evaluated by scoring the time for completion in seconds, using one trial only.

Although research indicates that TMT performance, as in RT, is slower in older compared to younger adults [33, 40], with additional slowing related to pathological aging such as MCI, AD [41, 42], and vascular dementia [43] (but see also [10, 15, 21, 41, 44–54]), there are potential limitations associated with the clinical use of the TMT. Although Trails

tion processing and response, pos-
e of RT tests. RT tests arguably
ide more 'data rich' results than
nore the fact that the TMT is pen
so means that it is difficult to use
l format in conjunction with neu-
and many other imaging studies
l response with underlying phys-
ee Müller et al. [36] and Hagen et

e time it takes to administer the
nisticated and function-specific RT
y test (and one typically used in
dies) could be administered using
nterfaces of computers, laptops,
ogy devices (e.g., tablets). Poten-
such technology can permit the
mediate availability and electronic
for interpretation and comparison
lts. Taking this concept one step
vice technology means that clini-
esearch-based RT testing does not
med within a clinical setting and
ly require someone to administer

or research focus in aMCI relates
or disproportionate RT slowing
the increased risk of developing
rally ignored fact remains that irre-
substantially slowed information
ponse may have significant detri-
n daily living. Arguably, in terms of
and clinical relevance, measuring
with respect to TMT performance
egradation in the integrity of the
d in rapid responses to constantly

We address this question by investigating two measures commonly used as indicators of processing speed in aMCI and AD, namely the TMT, sometimes used in clinical assessment, and the RT component of a form of visual search test commonly employed in research and specifically that is used in a series of previous studies by Tales and colleagues (e.g., [8]), in which RT to a target appearing in isolation is compared to the time taken to respond to the same target when it is surrounded by distracting information. These tasks are similar to Trails B and Trails A, in that they are generally assumed to involve complex and higher processing levels and varying loads, attention shifting, eye movements, sequencing, suppression and inhibition of irrelevant or previously attended locations and stimuli, but unlike the TMT, numerous trails are presented in quick succession (as described in the methods section to follow). We examine in the first instance whether the visual search based RT tests can at least match the ability of the TMT to differentiate aMCI from cognitively healthy aging at group level. Secondly, as aMCI is a clinically heterogeneous group typically containing a proportion of individuals for whom aMCI represents the early stages of a dementing process, a proportion for whom it remains of unknown etiology and others for whom it is a temporary condition, we examine the ability of each test to provide intra-group variation in performance. As both disproportionately slower task-completion time and RT are related to the presence of dementia, one would expect to see some performance variability within the aMCI but not the cognitively healthy control group in both tests.

Research has also indicated that in older adults both age and educational level can influence TMT

ls are included in all tests so direct
rformance can be made.

conducted according to the princi-
ion of Helsinki. It was approved by
n Ethics Committee and all partic-
n informed consent to participate.
with the capacity to consent were
to consent was assessed by the
n specialist expertise in this field
h the requirements of the Mental

elling cognitively healthy older
nts with aMCI$^+$ (multi-domain
re recruited via the Bristol Memory
All had normal or corrected-to-
edication could not be controlled
rticipants were receiving medica-
n deemed likely to affect cognitive
elated function and those with
aving no drug treatment or inter-
condition, none were classed as
ssed. All participants performed
Memory Disorders clinic battery
gical tests including Mini-Mental
(MMSE) [72], WAIS-III (Wech-
ence Scale) subtests (digit span,
e completion) [73], Hopkins Ver-
-Revised [74], CLOX (executive
k) [75], Visual Form Discrimi-
NART [68], S word fluency and

neurological or psychiatric condition (see Phillips et al. [8] and [80, 81]). In total, 87 individuals took part in this research, 48 older adults with mild cognitive impairment and 39 cognitively healthy older adult controls[1]. The demographic details are shown in Table 1.

The cognitively healthy older adult and the aMCI$^+$ groups did not differ significantly with respect to mean Age [$Z = -1.65$, $p = 0.098$] or mean Educational level [$Z = -0.53$, $p = 0.6$], indicating that attempts at matching these demographics between groups was successful. However, the NART score (level of pre-morbid intelligence) was significantly poorer for the aMCI$^+$ compared to the cognitively healthy older adult group [$Z = -3.3$, $p = 0.001$]. As expected, MMSE score was significantly lower for the aMCI$^+$ compared to the cognitively healthy older adult group [$Z = -2.98$, $p = 0.003$].

Experimental task and procedure

In a counter balanced procedure, the TMT (both Trails A and Trails B) and the visual search task (both target alone and target plus distracter conditions) were administered to all participants by a trained psychometrist. Testing took place within the Bristol Memory Disorders Clinic.

The pen and paper TMT

When administering Trails A, the psychologist provided the participants with a practice sheet as a way of visually explaining the task. Once the participants completed the practice sheet, they completed the full Trails A. For this task the participants were instructed to draw one continuous line joining a series

Table 1
Demographic details

		Education	Age	NART	MMSE
tively healthy older adults ($n = 39$)	Mean	14.56	70.5	118.3	27.1
	SD	3.1	8.3	8.1	1.5
	SEM	0.49	1.3	1.3	0.2
($n = 48$)	Mean	14.4	67.6	111.8	25.9
	SD	3.72	8.6	16.6	1.8
	SEM	0.54	1.2	2.4	0.25

re immediately informed and they rrect them. Errors like this were he time to complete the task or if plete the task in the allotted time.

ed Visual Search Task

ch task used was one employed s studies by Tales and colleagues o 7], in which the time taken to (namely to discriminate whether pointing to the left or right) when lation upon the computer screen n to respond to the same target nded by similar but irrelevant and was determined. This paradigm a Toshiba Satellite-Pro lap top at a distance of 57 cm. Superlab Corporastion San Pedro, CA) was mulus presentation and response ce RT task included a black tar- or left-pointing arrow head; with ed to indicate whether the arrow- to the left or right. The distracting f seven black arrow-heads point- own. A 'clock-face' configuration d to position the target, both when

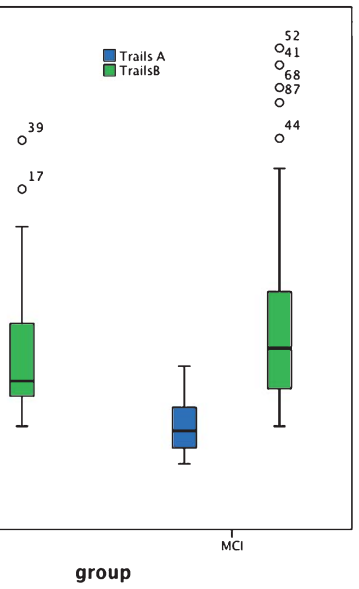
at each of the possible 'clock-face' locations giving a total of sixty-four trials. Distracters were presented for half the trials. On each trial the central fixation cross appeared on screen for 1000 ms prior to the appearance of the target and remained on screen for the duration of the trial. The stimuli remained on screen until a response was made. Participants were instructed to fixate on the center cross at the beginning of each trial and to respond as quickly but as accurately as possible as to whether the target was pointing to the right or left by pressing one of two computer keyboard keys. After instruction, all participants were asked to explain the task to the researcher in order to demonstrate that they fully understood the task and then performed approximately 10 practice trials. The ability of the participants to fixate upon the central cross was checked at the beginning of each trial by researcher observation. The researcher was also in a position to record any lack of trial response and to prompt re-engagement of the task. Participants received no performance-feedback during testing.

DATA ANALYSIS AND RESULTS

Group mean analysis for RT speed was based on the mean values (of correct trials only) for each indi-

Table 2
Normality of distribution (Shapiro Wilkes test)

	OLD			aMCI+		
	statistic	df	Sig.	statistic	df	Sig
	0.939	39	0.036	0.941	48	0.017
tion	0.953	39	0.104	0.911	48	0.002
	0.924	39	0.012	0.764	48	0.000
E	0.950	39	0.085	0.932	48	0.008
: target alone	0.911	39	0.005	0.944	48	0.022
: target & distracters	0.949	39	0.077	0.911	48	0.001
A	0.973	39	0.459	0.942	48	0.019
B	0.833	39	0.000	0.822	48	0.000



ils A and B performance based on individ-
onds).

tistical analysis was employed in

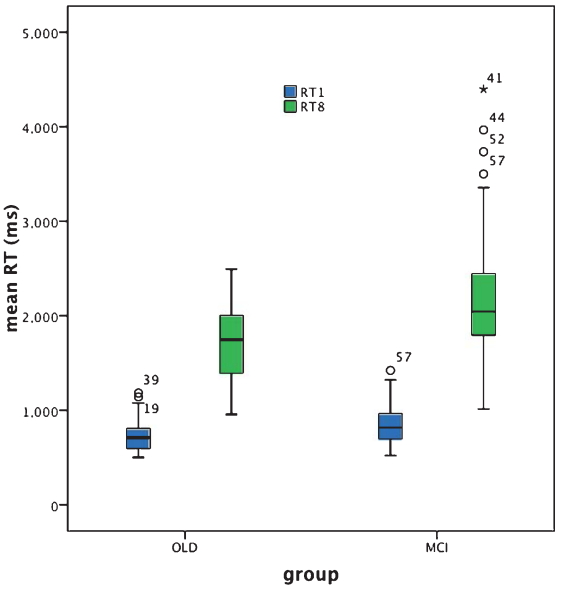


Fig. 3. Box plot for target alone (RT1) and target plus distracters search (RT8) performance based on individual reaction time (RT) (ms).

aging [$Z = -1.96$, $p = 0.05$; effect size (r) $= 0.21$]. For both groups, performance of Trails B was not

Table 3
) for the TMT (Trails A and B) and the mean RTs (ms) for the target alone and the target plus distracter visual search , together with the corresponding standard deviation (SD) and standard error of the mean (SEM)

	Trails A Mean response time (s)	Trails B Mean response time (s)	Search Target alone Mean RT (ms)	Search Target & distracters Mean RT (ms)
	35.9	78.7	744.2	1730.6
SD	10.4	34.7	172.9	402.9
EM	1.7	5.6	27.7	64.5
	40.6	98.2	861.1	2230.4
SD	13.8	51.6	209.2	709.9
EM	2.0	7.5	30.2	102.5

gnitively healthy older adult group
6; effect size (r) = 0.3]. For both
normally distributed and was not
lated with age, education, NART
all p-values >0.05].
the target plus distracters Visual
RT was significantly slower for
ed to the cognitively healthy older
3.5, $p < 0.001$; effect size = 0.38].
ance of this task was normally dis-
gnitively healthy older adult group
e for the aMCI$^+$ group. RT was not
ated with age, education, NART or
p-values >0.05] in either group.

es in the cognitively healthy older
not differ significantly in mean
Trails A [$Z = -0.745$, $p = 0.45$] or
186], or in RT for the target alone
96] or target plus distracters Visual
0.787, $p = 0.43$].

DISCUSSION

The TMT is sometimes used clinically to assess the speed of information processing in dementia, MCI, and related disorders, by measuring the time taken to complete the task of consecutively joining a series of numbers and or letters on a sheet of paper. However, in research terms, speed of information processing is generally described with respect to reaction time, i.e., the time elapsed between the relatively rapid presentation of a stimulus and the behavioral response, measured over a number of trials at relatively short intervals. Arguably, the processing involved in processing and responding to such rapid and repeated stimuli is different from that involved in performing the TMT, and we suggest that measuring RT may indeed be more akin to, ecologically valid or relevant with respect to the investigation of the integrity of information processing speed related to every day tasks which typically require rapid processing, decision making, and response.

However, although RT tests may, in theory, repre-

examined the ability of each test to
variation in performance. As both
slower task-completion time and
e presence of dementia, one would
performance variability within the
cognitively healthy control group

formance

mance failed to significantly dif-
from cognitively healthy aging at
ably this result is indicative of a
of the Trails A test to the pres-
eed the box plot (Fig. 2) reveals
ne results are for the patient and
rthermore, response time was nor-
for the cognitively healthy older
the aMCI$^+$ group (see Table 2).
al heterogeneity of aMCI$^+$, in that
on of such individuals would be
the prodromal stages of demen-
lly acknowledged accompanying
e time, the relative lack of individ-
esponse time within this group is

s B performance significantly dif-
from cognitively healthy aging.
response time is clearly slowed for
red to the control group and there
dividuals within the aMCI$^+$ group
e is represented by clear outliers.
presents the within-group hetero-
expect from such an etiologically
ever, Trails B also reveals hetero-
nce within the cognitively healthy

ertheless, the effect size of the significant difference in performance between the two groups was greater than that for the Trails B test (effect size 'r' $=0.21$ and 0.3), respectively.

For the target plus distracter visual search task, mean RT was significantly slower in aMCI$^+$ compared to cognitively healthy aging. The effect size of this outcome ($r=0.38$) was greater than that exhibited for the target alone search ($r=0.3$) and the Trails B ($r=0.21$) tasks, indicating that the target plus distracter visual search task is the one most sensitive to aMCI$^+$. Furthermore, whereas the distribution of RT performance was normal within the cognitively healthy older adult group for the target plus distracter visual search task this was not the case for the aMCI$^+$ group, revealing instead a number of considerably slower responses, i.e., outliers (see the Box plot in Figs. 2 and 3, and Table 2). There is, of course, once again some degree of overlap between performance in the control and the patient group and therefore not everyone with aMCI$^+$ reveals slower mean RT compared to cognitively healthy aging. It appears rather that the aMCI$^+$ group contains a greater proportion of individuals with disproportionately slower, responses. However, unlike Trails A, Trails B, and the simple target alone visual search RT task, the target plus distracter visual search RT task promotes outliers, i.e., disproportionately slowed responses only within the aMCI$^+$ group. It may be the case that this RT task does not produce as many 'false positives' i.e., disproportionately poor performance within the control group, as does the target alone search RT task and the Trails B test. Note also that three individuals in the aMCI$^+$ group are outliers in both the Trails B and the target plus distracter visual search RT test. This may indicate

present a decline to dementia if
ministered to an individual over
w up of all the participants in this
s from making such an analysis.
y within the aMCI$^+$ may, how-
ast in part, some of the disparity
tween previous studies, as slow-
to specific etiologies of aMCI$^+$,
h have a neurodegenerative basis.
ver, that a proportion of individu-
ave very slow RTs, much beyond
th cognitively healthy aging, indi-
individuals processing related to
es in the environment and situa-
life that require serial, rapid, and
processing, and response can be
red. These effects are of potential
ctive of whether an individual with
ly stages of dementia or not.

ation, IQ (NART), and MMSE

d difference in performance was
in the aMCI$^+$ group. RT was
for males than females for the tar-
arch group. Although there was a
r educational level for males than
oup, which may have potentially
s result, there was no significant
n educational level in either males
T and it remains to be seen why
ffect should be evident in the tar-
earch task RT only. Nevertheless
lts indicates that within the same
rocessing speed outcome and its
may be influenced by the test used

tionship occurs only when a wider range of ages is included. In contrast, although performance of Trails B was not significantly correlated with age in the control group, it was significantly correlated with age (surviving Bonferroni correction) in the aMCI$^+$ group: a finding which if further research finds to be robust, may have implications for the interpretation of results over this age range. The finding that age is not similarly correlated with performance in both cognitively healthy aging and aMCI$^+$ also breaks an assumption necessary for covariate analysis (if parametric analysis of RT data is attempted; another reason why we used non-parametric testing for our results). In contrast to Trails A and B, RT of both versions of the visual search task was not significantly correlated with age for either the cognitively healthy older adult or the aMCI$^+$ groups.

Performance of Trails A, B, and both versions of the visual search RT task was not significantly correlated with educational level for either the cognitively healthy older adult or the aMCI$^+$ groups (although there was some evidence of a correlation for Trails A performance and education for the aMCI$^+$ group it did not survive Bonferroni correction). Although the aMCI$^+$ group had a significantly lower IQ (NART score), explained by the lower score for females compared to males in this group, performance of none of the four tasks was significantly correlated with IQ. Performance of TMT and both visual search tasks was not significantly correlated with MMSE (note however that for the aMCI$^+$ group, Trails B was significantly correlated with MMSE score but again this did not survive Bonferroni correction).

There is therefore some room for debate about whether some relatively small effects of age and edu-

itations

ve were unable to follow up both
determine clinical outcome thus
s of whether those individuals with
imes and RTs in the aMCI$^+$ group
o develop dementia. Furthermore,
he results and thus their potential
ed by the fact that we did not test
tedly and over various time peri-
uld have combined our behavioral
ging study in order to determine
tween our RT and response speed
ral and functional integrity both
vidual level. We would have also
t of methodological manipulations
s time pressure, processing load,
of distraction in order to explore
range of information processing

e only measured response speed
it would have been useful to deter-
ty of such tests to aMCI and to
e decline, conditions that may rep-
s on a continuum between health
peating this study with a larger
ider range of demographic factors
er investigation in to the potential
en processing speed and RT and
e, IQ, educational level, and level
ment. Further research would also
range of processing speed and RT
d in research and clinically and in
such as practice effects.

he very fact that the search tests
e to aMCI$^+$ than the Trails B tests

ate between cognitively healthy aging and aMCI$^+$ at group level and in revealing a heterogeneity of performance one would expect from an etiologically heterogeneous disorder such as aMCI$^+$. These findings, together with evidence from previous studies regarding the relationship between RT and neurological status, indicates that RT tests should at least be included in the diagnosis and follow-up of cognitive impairment.

ACKNOWLEDGMENTS

BRACE-Alzheimer's Research [registered charity number 297965] and Maggie Agg for assistance in participant recruitment.

Authors' disclosures available online (http://j-alz.com/manuscript-disclosures/15-0791r2).

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